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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/151,612	09/11/1998	LEONARD D. KOHN	5616/3	8049

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	31

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/151,612	KOHN ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,11-18,21-25,29-60,62,67-78 and 80-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,11-18,21-25,29-35,42-46,60,62,74-76 and 81-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *22* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The request filed on 4/16/2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/151,612 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 1, 2, 4-10, 12-16, 18, 21-22, 24-26, 29-35, 43, 45-46, 60, 74-78 and 80-83 were amended and new claims 84-91 have been added in paper # 21 (7/1/2002).

3. Claim 33 was amended in paper # 24 (10/22/2002).

4. Claims 10 and 26 were cancelled and claims 1, 4-9, 11-13, 15, 17, 18, 21-25, 29-31, 33, 42, 44-46, 62, 75, 81, 84, 85, 87-91 have been amended in paper # 30 (8/5/2003).

5. Claims 36-41, 47-59, 67-73, 77 and 80 have been withdrawn from consideration in paper # 30 (8/5/2003).

6. Claims 1, 2, 4-9, 11-18, 21-25, 29-60, 62, 67-78 and 80-91 are pending.

7 The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

8 The following Office Action contains NEW GROUNDS of rejection.

Election/Restrictions

9. It is acknowledged that applicants have elected Group I with traverse in response to the restriction/election requirement in paper # 23 (9/9/2002), along with the following

species: A) a somatic cell and (ii) a fibroblast B) transfection C) the polynucleotide does not contain a stimulatory CpG motif and D) MHC class I in paper number 24 filed 10/22/2002. It is further acknowledged that applicants have elected (a) a protein as the species of antigen in paper # 29 (6/2/2003).

With respect to group restriction applicant's argue that all the claims in the present application involve the same basic ingredients: (a) obtaining a cell and (b) introducing a nonspecific double-stranded polynucleotide greater than 25 base pairs in length into the cell thereby activating expression of a gene or gene product which increases the ability of the cell to present antigen to an immune cell in a subject and would not impose a serious burden on the examiner. This is not found persuasive. The inventions are distinct because the methods of Groups I, III, VI, VII and VIII differ in the method objectives, and parameters and in the reagents used and have different endpoints. The products of Groups II, IV and V are structurally and functionally distinct. The products of Group II are DNA molecules greater than 25 bp in length (e.g. plasmids, oligonucleotides, chromosomes, genomic DNA, ect), whereas the products of Group V are different DNA sequences of 19-21 bp in length. The products of Group IV are pharmaceutical compounds including methimazole and tautomeric cyclic thiones.

As to the question of burden of search, the methods of Groups I, III, VI, VII and the products of Groups II, IV and V are classified in different classes and subclasses. The divergent classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of

search. Clearly different searches and different patentability issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made FINAL.

However, the election of species requirement is vacated and all species will be examined.

10. Claims 1-2, 4-9, 11-18, 21-25, 29-35, 42-46, 60, 62, 74-76 and 81-91 are under examination.

Information Disclosure Statement

11. The IDS filed 3/19/1999 has been partially considered. All U.S. patents and references 28, 52, 67, 74, 88 and 110 have been considered. All others have not been considered because they are not available with the application. If these references are supplied, they will be considered at that time. Additionally, reference 37 does not contain a publication date and will not be considered until the publication date is provided.

Specification

12. The Figures and Brief description of the Drawings are objected to for the following reasons.

a) The figures do not have figure numbers on the front of the figures. The figures need to have figure numbers on the front of the figures, corresponding to the brief description of the drawings.

b) Figure 2 has parts a, b and c, but the brief description of the drawings only describes figures 2A and 2B. A description for figure 2C needs to be added to the brief description of the drawings.

c) Figure 6 has parts a and b. A description of figures 6A and 6B need to be added in the brief description of the drawings.

Appropriate action is requested.

Rejections Withdrawn

13. The previous rejection (paper # 15, mailed 10/12/2001) of claims 1-2, 4-18, 21-26, 29-35, 42-46, 60, 62, 74-78 and 80-83 under 35 U.S.C. 112, first paragraph, enablement has been maintained in part and made again (see Response to arguments for rebuttal and New Grounds of rejection). The rejection of claims 10 and 26 under 35 U.S.C. 112, first paragraph has been withdrawn because claims 10 and 26 have been cancelled in paper # 30 (8/5/2003). The rejection of claims 77 and 80 under 35 U.S.C. 112, first paragraph has been withdrawn because claims 77 and 80 have been withdrawn from consideration in paper # 30 (8/5/2003). The rejection of claim 78 under 35 U.S.C. 112, first paragraph has been withdrawn because claim 78 is drawn to a nonelected invention.

14. The previous rejections (paper # 15, mailed 10/12/2001) of claims 1-2, 4-18, 21-26, 29-34, 42-46, 66, 74-78 and 80-82 under 35 U.S.C. 112, second paragraph have been withdrawn in view of applicant's amendments to the claims. The rejection of claims 10 and 26 under 35 U.S.C. 112, second paragraph has been withdrawn because claims 10 and 26 have been cancelled in paper # 30 (8/5/2003).

15. The previous rejection (paper # 15, mailed 10/12/2001) of claims 1-2, 4-6, 13, 23, 25 and 44 under 35 U.S.C. 102(b) as being unpatentable over Stacey et al (J. Immunology 157; 211602122, 1996) has been withdrawn because of applicant's arguments and amendments to the claims. Stacey et al do not teach *ex vivo* introduction of nonspecific double-stranded polynucleotides in nonimmune mammalian cells by transfection and re-introduction of the mammalian cells into a subject as a therapeutic method.

16. The previous rejection (paper # 15, mailed 10/12/2001) of claims 1-2, 4, 6, 10, 13, 16 and 74 under 35 U.S.C. 102(b) as being unpatentable over Henderson et al (J. Immunology 159; 635-643, 1997) has been withdrawn because of applicant's arguments and amendments to the claims. Henderson et al do not teach *ex vivo* introduction of nonspecific double-stranded polynucleotides in nonimmune mammalian cells by transfection and re-introduction of the mammalian cells into a subject as a therapeutic method.

17. The previous rejection (paper # 15, mailed 10/12/2001) of claims 1-2, 4, 6, 8, 13 and 42 under 35 U.S.C. 102(b) as being unpatentable over Fuller et al (AIDS Research and Human Retroviruses 10; 1433-1441, 1994) has been withdrawn because of

applicant's arguments and amendments to the claims. Henderson et al teach do not teach the *ex vivo* introduction of nonspecific double-stranded polynucleotides in nonimmune mammalian cells by transfection and re-introduction of the mammalian cells into a subject as a therapeutic method

18. The previous rejection (paper # 15, mailed 10/12/2001) of claims 1, 8 and 17 under 35 U.S.C. 103(a) as being unpatentable over Stacey et al in view of Brakebusch et al (J. Biol. Chem. 272; 3764-3682, 1997; PTO-1449, #15) has been withdrawn because of applicants amendments to the claims and withdrawal of Stacey et al (see item # 15 above).

Response to Arguments

19. The previous rejection of Claim 35 under 35 U.S.C. 112, second paragraph is maintained. There is insufficient antecedent basis for "the host animal" recited in claim 35.

20. The previous rejection of Claim 35 under 35 U.S.C. 112, first paragraph is maintained in part and made again (see a-d below and New Grounds of Rejection). Applicant's arguments related to the rejection of claims 1-2, 4-18, 21-26, 29-35, 42-46, 60, 62, 74-78 and 80-83 under 35 U.S.C. 112, first paragraph in the response filed in paper # 21 (7/1/02) have been fully considered, but are not found persuasive. The response recites that the claims are enabled for the entire scope of the claims and requests the examiner to reconsider the instant invention in two parts: (1) can the invention achieve an immune response *in vivo* that is readily reproduced by scientists

skilled in the art and (2) can the immune response be therapeutic (see New Grounds of Rejection below).

a) With respect to applicant's arguments that DNA vaccines are different from the technology of the instant application because DNA vaccines require expression of an antigen encoded by the administered DNA. Applicant's argument has been fully considered, but is not found to be persuasive. Due to the indefinite nature of the phrase "nonspecific double-stranded polynucleotides" (see 112, 2nd (b)), the claims in the instant application are still broadly drawn to methods that encompass DNA vaccines. It is acknowledged that applicant's invention is not intended to encompass DNA vaccine technology, however, the claims as written still encompass this limitation.

b) With respect to applicant's arguments that the claimed methods do not encompass in vivo administration of a "nonspecific double-stranded polynucleotide" applicant's arguments are not found persuasive. Claim 11 and those claims that depend from claim 11 encompass an *in vivo* method which recites introduction of a nonspecific double-stranded polynucleotide " into the cell within the subject" as a method of increasing immune recognition.

c) With respect to applicant's arguments that the "route of delivery" is not critical to the claimed methods is not found persuasive in view of the teachings of Morse et al (Cancer Research, 1999, 59; 56-58) (see 112 first paragraph below under New Grounds of rejections) because Morse et al show that "dendritic cells injected intravenously localized in the lungs and then redistributed to the liver, spleen, and bone marrow, they were not detected in lymph nodes or tumors" (see abstract).

d) With respect to applicant's arguments that "any double-stranded polynucleotide" will work in the instantly claimed invention, applicant's arguments are not found persuasive. Applicants respectively admit that further experimentation may be required by stating "because some experimentation may be required that does not rise to the level of undue experimentation" (see page 20, second paragraph of applicants response filed 7/2/2002). Furthermore, with respect to the adaptation of the Shimojo model and the assertion that the specification in light of the Shimojo model adequately teaches one of ordinary skill in the art how to choose operative from inoperative "nonspecific double-stranded polynucleotides".

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of using any double-stranded polynucleotide to increase immune recognition in a subject for treating any tumorous or infectious disease, for those skilled in the art to experiment with the claimed method as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what species of "nonspecific double-stranded polynucleotides" are required for increasing antigen presentation and immune recognition for treating any tumorous or infectious disease, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from guidance in the specification to the full breadth of the claimed invention. Therefore, the as-filed specification is not enabled for the full scope of the claimed invention.

The following are NEW GROUNDS of rejections

21. Claims 1, 2, 4-6, 7-9, 11-18, 21-25, 29-32, 34-35, 42-45, 62, 74-75, 84, 86, 90 and 91 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicants regard as their invention.

a) Claims 1, 2, 4, 5, 7, 8, 11 and dependent claims 6, 9, 12-18, 21-25, 29-32, 34-35, 42-45, 62, 74-75, 84, 86, 90 and 91 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claims 1, 2, 4, 5, 7, 8 and 11 are indefinite for reciting incomplete method claims, which do not clearly set forth method steps and do not include a resolution step, which reads back on the preamble of the

claimed method. Merely obtaining a nonimmune or immune cell or monocyte or dendritic cell, introducing a sequence "nonspecific double-stranded polynucleotide" into the cell *ex vivo* or in vivo (claim 11) and re-introducing the cell into a subject does not result in a method of increasing immune recognition. The claims should conclude with a step of measuring immune recognition of a nonimmune or immune cell or monocyte or dendritic cell in a subject in parallel with a control in which the mammalian cells are transfected in the absence of the "nonspecific double-stranded polynucleotide", for example, thereby producing the method of increasing immune recognition relative to an established baseline (i.e. control) as required by the preamble, which recites "a method of increasing immune recognition of a mammalian cell in a subject".

b) Claims 1, 2, 4, 7, 8, 11, 60, 76, 81, 83 and dependent claims 6, 9, 12-18, 21-25, 29, 31-32, 34-35, 42, 43-46, 60, 62, 74-75, 82, 84-90 are indefinite for reciting "nonspecific" in claims 1, 2, 4, 7, 8, 11, 60, 76, 81 and 83. It is unclear what is contemplated by the term "nonspecific". Does the term "nonspecific" mean that the double-stranded polynucleotide is a coding polynucleotide, a noncoding polynucleotide, encodes a polypeptide not involved in antigen presentation or increasing an immune response, contains only nucleotide analogues, or is more than one polynucleotide contemplated in the method, whereby one of the polynucleotides is "nonspecific"? What is the "nonspecific double-stranded polynucleotide" nonspecific for? As written, the metes and bounds of the claims cannot be determined.

c) Claim 85 is indefinite for reciting "The method of claim 76". There is insufficient antecedent basis for "The method of claim 76" because claim 76 is a vaccine and not a method.

d) Claim 25 is indefinite for reciting "does not initiate such antigen presenting response by acting through a cell surface receptor". It is unclear what antigen presenting response is contemplated that doesn't require antigen in association with the major histocompatibility complex (MHC), allowing recognition by the T cell receptor. Herbert et al (The Dictionary of Immunology, 1995, Academic Press Limited, 4th ed, page 11) define antigen presentation as "the presence on the surface of a cell of antigen in a form that allows its recognition by the T cell receptor. This usually requires that the antigen be presented as a small peptide in the groove of a syngeneic MHC antigen molecule". How does a cell present antigen without acting through a cell surface receptor?

e) Claims 29, 60 and dependent claims 9 and 12 are indefinite for reciting "treating the cells to prevent cell division" in claims 29 and 60. It is unclear what cell treatment or treatments are contemplated by the method. Are the cells viable following treatment and what are the cells treated with that prevents cell division?

f) Claim 7 and dependent claim 90 are indefinite for reciting "does not contain a CpG motif" in claim 7. Dependent claim 90 recites "methylation of any CpG motifs", which is contradictory to claim 7. Does the polynucleotide contain CpG motifs or not?

g) Claim 16 is indefinite for reciting "introduction of concentration". The phrase "introduction of concentration" does not appear to be proper and it is unclear exactly what is meant by the phrase. Applicant is requested to clarify.

h) Claim 62 is indefinite for reciting "or an antigen presentation". The phrase "or an antigen presentation" does not appear to be proper and it is unclear exactly what is meant by the phrase. Applicant is requested to clarify.

22. Claims 1-2, 4-5, 7-9, 11, 24, 25, 43-46, 60, 76, 81, 83 and dependent claims 6, 12-18, 21-23, 29-35, 42, 62, 74, 75, 82 and 84-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-2, 4, 7-9, 11, 24, 25, 43-46, 60, 76, 81, 83 and dependent claims 6, 12-18, 21-23, 29-35, 42, 62, 74, 75, 82 and 84-90 are broadly drawn to a large genus of "nonspecific double-stranded polynucleotides" and members of the genus are variable in size and chemical composition. Therefore, many structurally unrelated polynucleotides are encompassed within the scope of these claims, including double-stranded DNA, double-stranded RNA, chromosomes, and fragments and analogues of the "nonspecific double-stranded polynucleotide" species. The claims, as written encompass "nonspecific double-stranded polynucleotides", which vary substantially in length, nucleotide composition and structure. The specification does not provide

sufficient written description as to the structural elements of "nonspecific double-stranded polynucleotides" or the nexus between "nonspecific double-stranded polynucleotides" and increased immune recognition of a mammalian cell. The specification does not describe the organization, location or actual polynucleotide sequences of functional elements within the "nonspecific double-stranded polynucleotides" correlative to increasing immune recognition in a mammalian cell. For example, some of the "nonspecific double-stranded polynucleotides" do increase MHC class I and Class II expression and some "nonspecific double-stranded polynucleotides" do not increase MHC class I and class II expression (see Figures 1B and 2B). The specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed.

The Guidelines for the Examination of Patent Applications Under 35 U.S.C. 112, paragraph 1 "Written Description Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (Federal

Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

23. Claims 1-2, 4-9, 11-18, 21-25, 29-35, 42-46, 60, 62, 74-76 and 81-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 1, 2, 4-9, 11-18, 21-25, 29-35, 42-46, 74, 75, 84, 86, 90 and 91 are broadly drawn to methods of increasing immune recognition of a nonimmune cell or an immune cell or a monocyte or dendritic cell or a tumor cell by introducing a "nonspecific double stranded polynucleotide" (dsDNA, dsRNA, nonspecific ds polynucleotides) greater than 25 nucleotides in length wherein the polynucleotide contains CpG motifs (claims 8, 85, 90) or does not contain CpG motifs (claims 4, 7, 86) or is in addition to treatment with CpG motifs (claim 75) or introduction of a "nonspecific double-stranded polynucleotide" is in combination with an antigen (claim 2), RNA introduction (claim 18),

enhances another treatment (claim 62) and the polynucleotide is introduced into the cell *ex vivo* or *in* vivo (claim 11), thereby activating expression of a gene or gene product, wherein said activation increases the ability of the cell to present antigen to an immune cell and the cell is re-introduced into a subject for therapeutic benefit.

Claim 60 is drawn to a method for treating a mammalian disease which is sensitive to immunotherapy which comprises: (a) removing diseased cells from a mammal; (b) introducing a sequence non-specific double stranded polynucleotide greater than 25 nucleotides in length into the cells; (c) treating the cells to prevent cell division, but permitting other metabolic activity; and (d) immunizing the mammal with an effective amount of the cells to treat the symptoms of the disease; the same method used to enhance another treatment method that enhances an immune response or antigen presentation.

Claims 76, 81-83, 85, 87, 88 and 89 are directed to vaccines and methods for treating cancer which is associated with immunodeficiency (AIDS as a preferred embodiment) with a vaccine (claim 76) comprising a somatic mammalian cell with the enhanced ability to present antigen to the immune system, comprising introducing a sequence "nonspecific double stranded polynucleotide" greater than 25 nucleotides in length into the somatic mammalian cell *ex vivo*, which causes the cell to have an increased ability to present antigen increasing the expression of a MHC molecule or a co-stimulatory molecule involved in antigen presentation and preparing the mammalian cell for immunization; and introducing the cell into a subject.

The specification discloses that "nonspecific double-stranded polynucleotides" (DNA and RNA) introduced *ex vivo* into the cytoplasm of non-immune cells induced MHC gene expression and the expression of some other essential genes important for antigen processing and presentation in association with MHC. The declaration attached to Paper Number 21, filed 7/1/2002 by Dr. Kohn submits that administration of mitomycin-treated cells transfected in vitro with polyI-C and poly dIdC, 35 bp long, decreased thyroid tumor size in a rat model. The effect is not duplicated by single stranded nucleic acids, and it is different and additive to increased antigen presentation resulting from γIFN. The specification further discloses that a species of "nonspecific double-stranded polynucleotides" can induce the expression of the 90K tumor-associated immunostimulator implicated in host mechanisms to defend against tumors and AIDS, and that "nonspecific double-stranded polynucleotides" have a different regulation mechanism from that of γIFN (see Example 1). Additionally, the specification discloses that mice immunized with syngeneic fibroblasts transfected *in vitro* with "nonspecific double-stranded polynucleotides" and a functional thyrotropin receptor (TSHR), were induced to develop an autoimmune disease with features mimicking the human Grave's disease.

In vitro and animal model studies have not correlated well with *in vivo* clinical trial results in patients. Since the therapeutic indices of immunontherapeutic regimens can be species- and model-dependent, it is not clear that reliance on the generation of disclosing certain "nonspecific double-stranded polynucleotides" and their ability to increase immune recognition in certain experimental models (i.e. rat thyroid tumor

model) accurately reflects the relative ability of the broadly claimed methods and vaccines to treat any tumorous or infectious disease, as encompassed by the claims.

There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed methods to introduce any "nonspecific double-stranded polynucleotide" greater than 25 nucleotides in length into a mammalian cell as a method of increasing immune recognition through enhanced antigen presentation to an immune cell. Figure 1 in the instant application demonstrates that bacterial DNA, salmon DNA, calf thymus DNA, and DNA oligonucleotides from foamy virus and cytomegalovirus transfected into rat cells (FRTL-5) increased expression of MHC class I or MHC class II mRNA's relative to the control and mock transfections (see Figure 1B). However, cDNA and total RNA isolated from FRTL-5 cells did not increase mRNA expression of MHC class I or MHC class II when transfected into FRTL-5 cells (see Figure 1B). Further, transfer RNA did not increase mRNA expression of MHC class I and MHC class II (see Figure 1B). Figure 2B in the instant disclosure shows that FRTL-5 cells transfected with poly(dA), poly(dC), poly (dT), poly (A), poly (C), and poly (U), 25 bp to 54 bp in length, do not increase mRNA expression of MHC class I or MHC class II in FRTL-5 cells (see Figure 2B).

Additionally, Boczkowski et al (Journal of Experimental Medicine. 184: 465-472, 1996) disclose that dendritic cells transfected in vitro with total RNA (encoding and noncoding dsRNA) and polyA+ RNA isolated from E.G7-OVA (EL4 cells transfected with the cDNA of chicken ovalbumin) or EL4 cells only induced potent OVA-specific

cytotoxic T lymphocyte (CTL) response in the case of the E.G7-OVA RNA's. Dendritic cells transfected with EL4 RNA's did not induce a CTL response.

Efficient antigen presentation and induction of an immune response by dendritic cells or nonimmune cells, the number and stability of MHC class I-peptide complexes is crucial. Because effective or defective antigen presentation determines the type and degree of immune resonse that is induced, ranging from immunity to tolerance presentation of tumor antigen alone may not suffice for the generation of immunity, but may depend upon the type of antigen (immunogenic or nonimmunogenic), the expression of co-stimulatory molecules and the functional state of the nonimmune or immune cell or monocyte or dendritic cell that is used (Grabbe et al. Immunology Today. 16(3): 117-121, 1995). It is unclear how simply activating or upregulating the expression of a gene or gene product by any "nonspecific double-stranded polynucleotide" as recited in the claims will increase immune recognition in a subject, which relies on a complex series of immunological events *in vivo* such as priming of cytotoxic T lymphocytes by co-stimulatory signals provided by the interaction between CD80 and CD86 (B7) molecules on professional antigen-presenting cells and CD28 molecules on T cells as well as other co-stimulatory molecules (CD23, CD11a, CD11c, LFA-3 and ICAM-1). While the obvious goal of the claimed methods is to increase immune recognition, the complexity of the immune system and the factors that govern T cell mediated immunity makes elucidating the preferred method far more complicated than just defining the desired outcome. Applicants have provided insufficient objective evidence that any "nonspecific double-stranded polynucleotide" would predictably

enhance MHC class I and class II expression on cells and result in increased immune recognition *in vivo*.

With respect to tumor treatment methods applicant has shown that polyI-C and poly dIdC injected into thyroid tumor cells *ex vivo* and re-introduction of the transfected thyroid tumor cells into rats showed a decrease in tumor size.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell reviews the current thinking on cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (J. NIH Research, 1995; 7; 46-49 see entire document, particularly the last paragraph). It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Forni et al (Cancer Research, 2000, 60; 2571-2575) disclose tumor cells have the ability to escape immune reactions and tumor masses can suppress immune attack. Mouse models show that elicitation of a significant immune response in patients with advanced tumors is exceedingly difficult, and only a minority of tumor-bearing mice are cured. "As a tumor increases in size, it becomes refractory to immunotherapy" (see page 2571, left column). A similar picture is emerging from Phase I immunotherapy trails where only a few patients with established tumors display objective and in any event temporary responses (see page 2571, right column). Forni et al further disclose that MHC molecules are polymorphic and different peptides would need to be prepared to fit in the polymorphic peptide-binding clefts of the many MHC class I and II molecules

(see page 2573). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy *in vivo*. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications. Furthermore, the escape of some tumors from immune recognition has been attributed to insufficient costimulatory signals and deficient antigen processing despite the presence of antigenic epitopes (Grabbe et al. Immunology Today. 16(3): 117-121, 1995). The effectiveness of an antigen-presenting cell to present antigen is potently modulated by cytokines, indicating that the local cytokine microenvironment is crucial for the generation and elicitation of tumor immune response (Grabbe et al. Immunology Today. 16(3): 117-121, 1995). Applicant's have not provided sufficient guidance with respect to methods of introduction of any "nonspecific double-stranded polynucleotide" and increasing MHC class I and class II molecules on the surface of nonimmune or immune cells resulting in increased immune recognition *in vivo* for any tumorous disease which are characteristically different.

Morse et al (Cancer Research, 1999, 59; 56-58) disclose that "dendritic cells injected intravenously localized in the lungs and then redistributed to the liver, spleen, and bone marrow, they were not detected in lymph nodes or tumors" (see abstract).

Applicant's have provided insufficient evidence that monocytes, immature or mature dendritic cells transfected with any "nonspecific double-stranded polynucleotide" and displaying increased MHC class I or class II molecules would be effective illicitors of antitumor immunity when re-introduced into a subject using any administration protocol.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability of increasing antigen presentation of tumors including non-immunogenic and weakly immunogenic tumors particularly tumor cells isolated from tumor bearing patients. The specification does not disclose how to extrapolate data obtained from observations on the increased expression of MHC molecules alone to the efficacy of treating any tumorous disease with any "nonspecific double-stranded polynucleotide" in a subject as broadly encompassed by the claims.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for increasing immune recognition by introducing any "nonspecific double stranded polynucleotide" into a cell that increases the cells ability to present antigen to an immune cell, commensurate in scope with the claimed invention.

Conclusion

24. No claim is allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Blanchard; whose telephone number is (703) 605-

1200. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,
David Blanchard.
703-605-1200

LARRY R. HELMS, PH.D
PRIMARY EXAMINER